REMARKS

Claims 2-8, 28-35 and 37-39 presently appear in this case. No claims have been allowed. The official action of October 29, 2003, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to a method for treating tumors in mammals or for inhibiting tumor cell proliferation in mammals by administering to a mammal in need thereof an effective amount of leptin or a mutein, fragment, or fusion protein thereof, or a salt or functional derivative thereof.

The examiner has objected to claim 9 as being a substantial duplicate of claim 29.

Claim 9 has now been deleted, thus obviating this objection.

Claims 2-9 and 28-39 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. With respect to claims 28 and 31, the examiner states that the claims recite "stringent conditions", but the claim does not include the definition of stringent conditions appearing at page 13, lines 12-15, of the specification.

The conditions recited at page 13 of the specification have now been inserted into claims 28-31, thus

clearly defining the stringent conditions and obviating this part of the rejection.

The examiner states that claims 2-8 recite method objectives but fail to either link said objectives to the method steps of the claims from which they depend, or provide active method steps to link the method objectives to the method of the claim upon which they depend.

Claims 2-8 have now been amended in order to insert a statement that links the method steps to the method objective, thus obviating this part of the objection.

Claims 2-9, 28 and 29 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Clark in view of Tanaka, Cohen and Stevenson. The examiner states that Clark teaches that breast cancer cell lines were inhibited by contacting with the tyrosine kinase inhibitors Herbamycin A and genistein, that such inhibitors decrease the association of Shc with Grb2, and that Herbamycin A can be administered *in vivo* with tolerable toxicity. The examiner concedes that Clark does not teach the administration of leptin for the inhibition of breast cancer cells or for the treatment of breast cancer. The examiner states that Tanaka teaches that a downstream effector of IRS-1 signaling is interaction with Grb2, that Grb2 binds to a phosphotyrosine residue in the YVNI motif on IRS-1 via its SH2 domain, that cellular

transformation induced by IRS-1 overexpression requires an interaction with Grb2, and that IGF-1 signals have been shown to promote tumorigenicity *in vivo*. The examiner states that Stevenson teaches that Grb2 complexed with mSos or Grb2 complexed with mSos and Shc transmits the extracellular signal for the activation of the Ras GTP/GDP exchange, that a component of this complex, Shc, is constitutively phosphorylated in several breast cancer cell lines, and suggests that the inhibition of the downstream signaling proteins of growth factor receptors is important. The examiner states that Cohen teaches that leptin downregulates the insulin-dependent tyrosine phosphorylation of IRS-1, and further that leptin attenuates the association of Grb2 with IRS-1. The examiner concludes that it would have been *prima facie* obvious to one of ordinary skill in the art to substitute leptin for Herbamycin A in the method of treating breast cancer, and that one would have been motivated to do so by the teachings of Tanaka on the correlation between IRS-1 signaling and tumorigenesis and the signaling of IRS-1 requiring interaction with Grb2 and the suggestion of Stevenson on the importance of inhibiting downstream signaling from growth-factor receptors in breast cancer. The examiner states that one of skill in the art would be motivated to substitute leptin for Herbamycin A or genistein because leptin

inhibits the association between IRS-1 and Grb2, and thus has the ability to inhibit the downstream signaling of IRS-1 taught to be important in tumorigenesis *in vivo* by Tanaka, and because leptin is an endogenous non-toxic protein that could be administered at higher doses than Herbamycin A, and thus be more effective at inhibiting the association between Grb2 and IRS-1. This rejection is respectfully traversed.

It is respectfully submitted that the examiner is engaging in a concerted attempt at hindsight reconstruction of the present invention. As stated in *Ex parte Levingood*, 28 USPQ2d 1300, 1300-1302 (Bd.Pat.Appl.&Int., 1993):

> That one can reconstruct and/or explain the theoretical mechanism of an invention by means of logic and sound scientific reasoning does not afford the basis for an obviousness conclusion, unless that logic and reasoning also supplies sufficient impetus to have led one of ordinary skill in the art to combine the teachings of the references to make the claimed invention. [Emphasis original]

Here, the only reference that the examiner cites relating to leptin is a paper from the laboratory of the present inventors, which shows that a variant form of the leptin receptor OB-R was found in human hepatocarcinoma cells and that exposure of these cells to leptin caused certain activities to be observed. There is no general teaching that leptin downregulates the insulin-dependent tyrosine phosphorylation of IRS-1 as suggested by the examiner. This

activity was only shown in very specific cells that have a specific OB-R variant thereon, i.e., HepG2 hepatocarcinoma cells. There is no suggestion in this reference that this is a general phenomenon in all cells of the body, or that contact of breast cancer cells with leptin would have similar effect. There is no suggestion that breast cancer cells have the same type of OB-R variant as HepG2 hepatocarcinoma cells. If breast cancer cells do not have a leptin receptor, why would it be expected that leptin would have any effect at all on such cells? Without evidence of the presence of such a receptor, the examiner has not made out a *prima facie* case of obviousness.

Furthermore, the examiner could not simply combine Clark, which is the only reference that deals with the treatment of breast cancer, with Cohen as the two references have no relationship whatsoever. It is necessary for the examiner to find two references that allegedly link the teachings of Cohen with the teachings of Clark based on abstract studies of signaling. The only motivation alleged by the examiner is that the Herbamycin A of Clark appears to be somewhat toxic, while leptin would not be considered to be toxic. However, this does not supply sufficient motivation for one to search through the literature of insulin receptor substrates. As in Tanaka, Clark has nothing whatsoever to do

with insulin receptor substrates. As stated in *In re Fritch*, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992):

> Here, the examiner relied upon hindsight to arrive at the determination of obviousness. It is impermissible to use the claimed invention as an instruction manual or "template" to piece together the teachings of the prior art, so that the claimed invention is rendered obvious. This court has previously stated "[o]ne cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention."

Here, it is only the present invention that mentions leptin. Anyone of ordinary skill in the art reading Clark, having a motivation to find a compound with the same properties as Herbamycin A that is less toxic, would not be led to leptin. The Cohen reference would not have been found in any such search, as it does not relate to breast cancer and Clark has nothing to do with IRS-1. At best, the examiner has provided a hindsight explanation of why the present invention might work. However, the motivation to combine these diverse references does not appear in the prior art.

In conclusion, there are two reasons why this combination of references would not have made the present invention obvious. First, it is an improper hindsight combination of references using applicant's invention as a template to find prior art that would explain the theoretical mechanism of the present invention.

A second and independent reason why the rejection must be withdrawn is that, even given the combination of references and the examiner's explanation, there would not have been a reasonable expectation that if leptin were substituted for Herbamycin A of Clark, the growth of breast cancer cell lines would be inhibited. There is no suggestion that the same type of OB-R leptin receptor appears on the breast cancer cells used by Clark, and therefore there is no reason to believe that leptin would exert the same effects on the breast cancer cells of Clark as was demonstrated on the hepatocarcinoma cells of Cohen. Furthermore, the theoretical explanation of the examiner is based on diverse experimentation in different references. Until the experiment is actually conducted and shown by experimental results to be successful, there would not have been a reasonable expectation that the substitution of leptin for Herbamycin A in the process of Clark would inhibit breast cancer cell growth.

Accordingly, for either of these reasons, Reconsideration and withdrawal of this rejection are respectfully urged.

Claims 2-9, 28, 29, 34 and 35 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Clark, Tanaka, Cohen and Stevenson as applied in the previous rejection, and further in view of Carter. The examiner states

that Carter teaches a fusion protein, termed an immunoadhesin, comprising the OB protein and the Fc domain of an antibody. The examiner states that the OB protein is synonymous with leptin, and that the Fc regions confer a longer half life on the OB protein. The examiner states that it would have been *prima facie* obvious to substitute the leptin immunoadhesin for leptin in the method rendered obvious by the combination discussed above. This rejection is respectfully traversed.

The examiner does not allege that Carter fulfills any of the deficiencies of the primary references discussed hereinabove. Accordingly, this rejection should be withdrawn for the same reasons as discussed above with respect to the rejection over the primary references. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

Claims 2-8, 28, 30-34 and 36-39 have been rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The examiner states that the claims are drawn to methods reliant upon the identity of a genus of leptin muteins and fragments having the ability to block cell proliferation. The examiner states that when given the broadest reasonable interpretation, the attribute of blocking cell proliferation is not limited to the mechanistic basis for the ability of leptin to block cell proliferation and inhibit tumor growth. Further, the examiner states that

the fragments would cover fragments that interact with other receptors or proteins to elicit inhibition of cell proliferation. This rejection is respectfully traversed.

The present specification at page 3, lines 16-18, refers to a test of the ability to block cell proliferation by the ability to inhibit the IGF-I-induced or insulin-induced proliferation of the human breast cancer cell lines T-47D and MCF7. As this is a reasonably specific test to determine whether any given mutein or fragment falls within the scope of the present invention, the claims have now been amended to explicitly include this test. If any given mutein or fragment passes this test, then it is a mutein or fragment in accordance with the present invention. While the claims do not require that these steps be carried out, the presence of this test in the claims serves as a definition, thereby effectively limiting the muteins and fragments only to those sharing the mechanistic basis for the ability of leptin to block cell proliferation and inhibit tumor growth. Accordingly, with this definition, the claims fully comply with the written description requirement of the first paragraph of 35 U.S.C. §112. Reconsideration and withdrawal of this rejection are respectfully urged.

The additional prior art cited as being pertinent to applicant's disclosure has been noted, as has the examiner's

implicit recognition that they are insufficiently pertinent to warrant their application against the claims.

It is submitted that all the claims now present in the case clearly define over the references of record and fully comply with 35 U.S.C. §112. Reconsideration and allowance are therefore earnestly solicited.

Respectfully submitted,

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